REMARKS

Claims 1-5, 7-9, and 16-19 were pending in the subject application. Claims 6, 10-15, and 20-26 were withdrawn. Applicants hereinabove have cancelled claims 6, 10-15, and 20-26, amended claim 16, and added new claims 27-28. Accordingly, claims 1-5, 7-9, 16-19, and 27-28 are pending and under examination in the subject application.

New claims 27-28 depend from amended claim 16, which is believed to fall within Group I, the Group provisionally elected by applicants in their July 16, 2003 response to June 16, 2003 Office Action. New claims 27-28 recite the same subject matter as claims 1, 16, and cancelled claim 14. Accordingly, support for new claims 27-28 may be found inter alia in the portions of the specification that support claims 1, 16, and cancelled claim 14.

Applicants hereinabove have amended the specification by adding a new first paragraph, which recites the instant application's chain of priority. The new first paragraph specifically refers to International Application No. PCT/US00/01957, filed January 25, 2000, from which the instant application claims the benefit of priority. This priority claim was made on page one of the transmittal letter which accompanied the instant application when filed on July 25, 2001 **(Exhibit A)**. International Application No. PCT/US00/01957 in turn claims the benefit of U.S. Provisional Application No. 60/117,099, filed January 25, 1999. This priority claim was made in Box No. VI of the first sheet of the original PCT Request **(Exhibit B)**. Accordingly, this Amendment raises no issue of new matter, and applicants respectfully request that it be entered.

Rejections under 35 U.S.C. § 102(a)

On page 4 of the November 14, 2003 Office Action, the Examiner rejected claims 1, 5, and 16-19 under 35 U.S.C. §102(a) as allegedly being anticipated by Tamilarasu et al., *J. Am. Chem. Soc.* **1999**, *121*, 1597. The Examiner alleged that Tamilarasu et al. discloses the preparation of Tat-derived oligoureas and meets all of the claimed limitations.

In response, applicants traverse the rejection and respectfully point out to the Examiner that a rejection under 35 U.S.C. §102(a) requires inter alia that the invention be described by *others* in a printed publication (italics supplied). Applicants note that the inventors of the subject application, namely Rana, Tamilarasu, and Huq, are also the same three authors of the above-indicated *J. Am. Chem. Soc.* publication. Applicants have attached as **Exhibit C** a copy of the declarations filed with the U.S. Patent and Trademark Office on November 21, 1999, indicating their inventorship of the subject invention.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection of claims 1, 5, and 16-19.

Rejections under 35 U.S.C. §102(e)

On page 3 of the November 14, 2003 Office Action, the Examiner rejected claims 1-5, 7-9, and 16-19 under 35 U.S.C. §102(e) as purportedly being anticipated by Rana et al., U.S. Patent No. 6,583,309 B1. The Examiner alleged that Rana and colleagues disclose the preparation of TAT-derived oligoureas and their utilization to inhibit TAT activities. The Examiner specifically pointed out columns 39, 40, and 48-52 of the '309 patent. The Examiner further alleged that the teaching meets all of the claimed limitations of the subject application.

In response, applicants traverse the rejection and respectfully point out to the Examiner that a rejection under 35 U.S.C. §102(e) requires inter alia that the invention by others be "patented or described in a printed publication... *before* the invention thereof by the applicant for patent." Applicants note that the subject application is a 35 U.S.C. §371 National Stage Application of International Application No. PCT/US00/01957, filed January 25, 2000, which claims the benefit of U.S. Provisional Application No. 60/117,099, filed January 25, 1999. The priority date of the subject application is thus January 25, 1999. The earliest effective U.S. filing

date of the '309 patent, on the other hand, is October 4, 1999, approximately eight months after the subject application's January 25, 1999 priority date.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-5, 7-9, and 16-19.

Rejections under 35 U.S.C. §102(f)

On page 3 of the November 14, 2003 Office Action, the Examiner rejected claims 1-5, 7-9, and 16-19 under 35 U.S.C. §102(f), alleging that applicants did not invent the claimed subject matter. The Examiner alleged that Rana et al., U.S. Patent No. 6,583,309 B1, teaches the instantly claimed invention. The Examiner noted that the '309 patent lists three inventors, including two of the inventors of the instant application. The Examiner further noted that the '309 patent also includes a third individual who is not a listed inventor in the instant application.

In response, applicants traverse the rejection and respectfully point out that the Examiner has provided no evidence to support a 102(f) rejection. The Examiner alleges that the '309 patent discloses the preparation of TAT-derived oligoureas and their utilization to inhibit TAT activities. The Examiner cited columns 39, 40, and 48-52 in support of this contention. The Examiner further alleged that this teaching meets all of the claimed limitations.

Applicants respectfully point out that the Examiner's citation fails to teach each and every element of the rejected claims. Applicants note that the '309 patent does not discuss "a synthesized oligourea comprising the basic-arginine rich region of TAT" and corresponding methods of use, as recited in applicants' claims 1-4. Neither does the '309 patent discuss a "synthesized oligourea comprising the sequence" of amino acid residues 48 to 57 of the TAT protein, and corresponding methods of use, as recited in applicants' claims 5, and 7-9. Finally, the '309 patent does not discuss a composition comprising an oligourea with amino acid side

chains corresponding in various ways to the TAT protein and its sequence of amino acids as recited in applicants' claims 16-19.

There is in fact only one reference in the '309 patent to the relevant portion of the TAT protein, and it is not presented in the context of discussing an aspect of the '309 invention. Rather, the '309 patent discusses this sequence only insofar as it is used as a means to evaluate the binding of the '309 compounds to TAR RNA (see columns 49-52 of the '309 patent). The binding of the '309 compounds was assessed by measuring their inhibition of TAR-TAT complex formation. In lieu of using the entire TAT protein, a shortened TAT peptide sequence was used in the assay: GRKKRRQRRR, i.e. amino acids 48-47 of the intact TAT protein. Binding ability of the '309 compounds was determined by measuring their inhibition of interaction of TAR RNA with this shortened TAT peptide sequence. Thus, instead of teaching this sequence of amino acids as being a component of the invention, the '309 patent mentions the sequence merely in the context of its role as a peptide against which the '309 compound competes for interaction with the TAR RNA.

As the Tat peptide sequence side-chain is neither disclosed nor taught as part of the '309 invention itself, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-5, 7-9, and 16-19.

Rejections under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1-5, 7-9 and 16-19 under 35 U.S.C. §112, First Paragraph. Applicants request that these rejections be withdrawn on the basis that applicants' specification as filed provides adequate support, as well as working embodiments, for both *in vivo* and *ex vivo* applications.

Regarding these rejections, the Examiner states the following:

The disclosure describes the preparation of Tat-derived oligoureas and their ability to inhibit HIV-1 Tat binding to the Tar element in a suitable in vitro binding assay. Appropriately drafted claim language directed toward in vitro binding methods would be acceptable. However, the full breadth of the claims encompasses in vitro and both in vivo and ex vivo clinical applications. However, the disclosure fails to support both in vivo and ex vivo applications at this point in time.

Applicants do not agree with the Examiner's statements, which allege that the disclosure of the present application fails to provide support for anything other than *in vitro* methods. As the Examiner is aware, prior to determining whether the disclosure satisfies the written description requirement for the claimed subject matter, a review of the claims and the entire specification should be made, including the drawings. Moreover, this analysis needs to be conducted from the standpoint of one of skill in the art at the time the application was filed.

Figure 4 of the present application and the description therefore at page 5, lines 10-19, provide clear support in the disclosure for *in vivo* inhibitory methods. Figure 4 depicts a working embodiment of the invention as it pertains to *in vivo* inhibitory methods. In particular, Figure 4 depicts inhibition of Tat transactivation by an oligourea derivative of the present invention *in vivo*. A person of ordinary skill in the art would immediately recognize that applicants had possession of the claimed invention, as it applies to both *in vitro,* as well as *in vivo* applications. Transactivation assays similar to the one depicted in Figure 4, which employ reporter systems, such as CAT, have been known in the art at least as far back as the 1980's (see, for example, Miesfeld, *et al.* (1986) Cell 46: 389-399.) Suitable protocols for carrying out these assays are well known to one of ordinary skill in the art. Moreover, applicants have used well-established terms to describe the *in vivo* assay of Figure 4. Such well-established terms or procedures do not have to be described in detail in the specification and should not be the basis of a rejection, based on the Written Description Guidelines. In the present assay, HL3T1 cells, which are a HeLa derivative cell line containing an integrated HIV LTR-1 promoter and CAT reporter gene, were used. Such cells are known in the art (see, for example, Felber and Pavlakis (1988) Science 239:184-186). These cells were transfected with the plasmid pSV2Tat (an expression plasmid

that contains the Tat coding region) and increasing amounts of the oligourea of the present invention. The plasmid pSV2Tat is also known in the art (Helland, et al. (1991) J. Virol. 65:4547-4549; and Bonifaci, Sitia and Rubartelli (1995) AIDS 9:995-1000). Luciferase was introduced (encoded by a plasmid), along with the expression plasmid and the oligourea compound, as a reference to normalize for transfection efficiency. Similar *in vivo* assays with different oligourea compounds have also been described in commonly-owned U.S. Patent No. 6,583,309 B1 at column 50, lines 18-40. Figure 4 of the present application shows CAT activity expressed from the integrated HIV-1 LTR of the HL3T1 cells with increasing amounts of an oligourea derivative according to the present invention, as compared to in the absence of the oligourea derivative. The results indicate that an oligourea of the present invention inhibits Tat transactivation. Since Tat transactivation requires the interaction of the trans-activation responsive region (TAR) RNA with the specific binding protein Tat, the oligourea can be said to have inhibited this interaction (i.e., binding) when it was introduced into a cellular environment wherein the inhibition was sought to occur. Therefore, applicants have provided a working example of an *in vivo* inhibitory method, as defined in applicants' claims.

The Examiner also alleges that the prior art teaches that the generation of successful HIV-1 antivirals is a difficult and unpredictable process. The Examiner states the following:

> **Several factors have contributed to antiviral failure including short serum half-lives, poor bioavailabilities, rapid clearance rates, sequestration of the drug by serum proteins, drug resistance to the quasispecies nature of HIV-1 infection, and the uneven distribution of the compound throughout the body (Gait et al., 1995). The disclosure fails to address any of these concerns.**

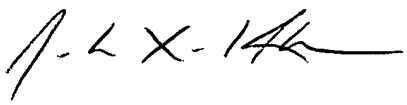
Applicants do not agree with the Examiner's allegations. The Examiner has recognized applicants' support for *in vitro* binding assays. Furthermore, applicants provide clear support in the disclosure for *in vivo* inhibitory methods, as well as working embodiments as they pertain to *in vivo* and *in vitro* applications. In particular, the *in vivo* assay depicted in applicants' Figure 4, shows the oligourea compound operating in a cellular environment reflective of the milieu where such compounds would be required to operate. Moreover, applicants specification teaches that

oligourea compounds of the present invention bind specifically to TAR RNA with high affinities (page 10, lines 9-14; page 11, lines 20-25) and form oligourea-RNA complexes which are stable when subjected to alkaline pH, high temperature, denaturing conditions, and protease digestion (page 12, lines 24-35; page 13, lines 1-11) -all desirable pharmacokinetic properties. Furthermore, as the Examiner is aware, applicants are not required to provide evidence of actual success in treating humans or animals for patentability. The requirements under the law for obtaining a patent should not be confused with the requirements for obtaining governmental approval to market a particular drug for human consumption.

In view of these remarks, applicants respectfully request that the Examiner withdraw the rejections under 35 U.S.C. §112, First Paragraph.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

Respectfully submitted,



John X. Haberman
Registration No. 55,236
Attorney for Applicants

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, NY 11797
(973) 331-1700